Medical Staff Conference

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Diabetic Microangiopathy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It sometimes seems that the rarer a metabolic disease is, the more clearly we understand its pathogenesis. Unfortunately the obverse also seems to hold true. Despite the work of many investigators the pathogenesis of diabetes mellitus remains obscure. We shall hear today from Dr. Marvin D. Siperstein concerning diabetic microangiopathy, the most important concomitant of diabetes and a field in which he has made many personal contributions.*

DR. SIPERSTEIN:† As every clinician who is responsible for the management of the diabetic is very well aware, the major *clinical* problem in the management of diabetes mellitus is *not* the control of blood sugar. Perhaps no more than 20 percent of all diabetic patients ever require insulin for the adequate control of blood sugar. Moreover, probably fewer than 5 percent of all persons with diabetes die as the direct result of hyperglycemia and other carbohydrate abnormalities of diabetes. By contrast, both pathological and clinical reports have amply demonstrated that approximately 85 percent of persons with diabetes die of the vascular disease of diabetes mellitus. It is, then, the vascular disease, not the carbohydrate abnormalities, that we in the clinic have to cope with.

These vascular manifestations of diabetes are (1) a relatively specific form of renal disease, intercapillary glomerulosclerosis, first described in its nodular form by Kimmelstiel and Wilson;[1] (2) atherosclerosis, the most common cause of death among adults with diabetes; (3) diabetic retinopathy, with its microaneurysms, and retinitis proliferans, which probably represent the second or third most common cause of blindness in the United States today and (4) the leg ulcers, gangrene and accompanying neuropathy, which represent the most common problems that plague the adult with diabetes. This, then, is diabetes mellitus as clinicians see it today, and as I suspect clinicians saw it even in the preinsulin era, though clearly it was not so recognized. Diabetic retinopathy, it should be recalled, was widely recognized by clinicians only in the past 30 years.

It is now apparent to everyone who follows diabetic patients that these manifestations of diabetes progress rather inexorably, regardless of the degree of control. By the end of the third decade of hyperglycemia, the Joslin Clinic and all other centers have found that retinopathy develops in 70 to 80

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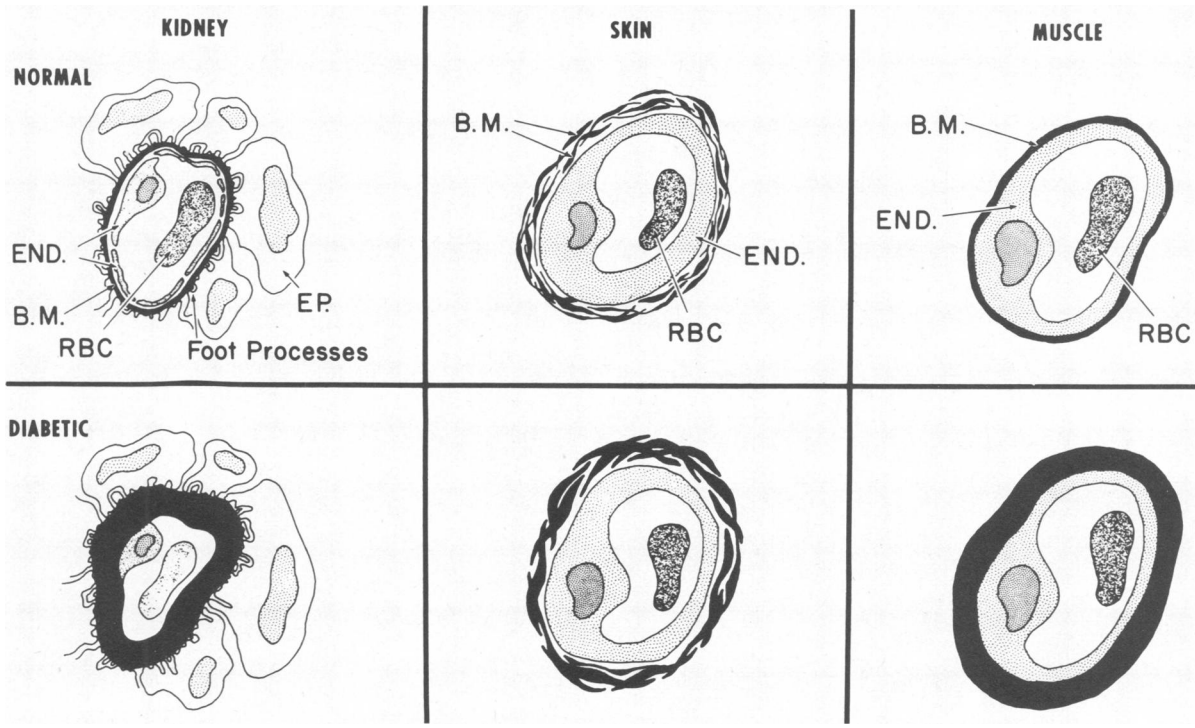

Figure 1.—Capillary basement membranes.

percent of persons with diabetes. I will not discuss today whether such an incidence curve can be shifted slightly to the left or a bit to the right by poorer or better control of the blood sugar. The fact remains that the best control does not prevent diabetic retinopathy. So the question that has been asked with particular intensity over the last two to three decades is, "what is responsible for the microangiopathy of diabetes?" What is its pathological basis and if possible what is its biochemical basis?

Clearly the major contributions to this field were first made with light microscopy by the ophthalmologist Friedenwald, who noted that the periodic acid-Schiff (PAS) positive nodule that Kimmelstiel and Wilson had described in 1936 really consists of a thickening of the capillary basement membrane. It was Friedenwald who first enunciated the unifying hypothesis that diabetic microangiopathy might be the equivalent of basement membrane thickening.[2] Bergstrand and Bucht[3] in 1957 and, independently, Farquhar, Hopper and Moon[4] at this institution two years later, reported that (as shown schematically in Figure 1) the earliest lesion in the diabetic kidney consists of a thickening of the basement membrane of the glomerular capillary. Such basement membrane hypertrophy progresses to engulf the epithelial and the endothelial cell and to encroach upon the lumen of the capillary. The pathological consequences of such basement membrane thickening in the kidney are obvious even by light microscopy. If this basement membrane thickening is focal, one sees the PAS-positive, nodular intercapillary glomerulosclerosis of Kimmelstiel and Wilson. If this process is diffuse throughout the kidney one sees under the light microscope the diffuse type of intercapillary glomerulosclerosis.

Measuring Basement Membrane Width

Everyone now agrees that the basic pathogenesis of diabetic renal disease involves thickening of the capillary basement membrane, be it peripheral or in the mesangial portion of the glomerulus. Many investigators, once these pioneering studies were published, asked the question, "can one quantitate diabetic microangiopathy by measuring the basement membrane width, and hence determine the degree of microangiopathy, in life?" Renal biopsy specimens are obviously difficult to obtain routinely, and the most accessible tissue, skin, has basement membranes that are laminated and difficult to quantitate. By contrast, as Zacks[5] was the first to show, muscle capillary basement membranes are relatively homogeneous, and (as shown again schematically in Figure 1) they demonstrate

thickening of the basement membrane just as does the kidney. The problem that became apparent to our group, consisting of Leonard Madison, Roger Unger and me, was how to obtain muscle during life and how to measure basement membrane widths reproducibly and objectively.

The first of these problems was solved relatively easily by adopting the Franklin-Silverman needle and taking a biopsy specimen from the quadriceps muscle halfway between the knee and the hip.[6-8] This is a fairly simple procedure, it takes five to six minutes, and it is probably less painful than a glucose tolerance test. The procedure has been generally adopted throughout the world, thereby eliminating the potential problem of interpreting variable results at different sites of biopsy. On the other hand there are unfortunately numerous methods of quantifying basement membrane width. The one that proved to be most objective and reproducible in our experience consists of overlaying 15 capillaries with 20 equidistant radiating lines, and at the point of contact of each of these lines with the basement membrane measuring this structure. The average of the 15 to 20 measurements is termed the quadriceps capillary basement membrane (QCBM) width.

Use of the QCBM Technique

While most of the several modifications of this technique that have been suggested yield adequate results, the only caution that must be observed is that the method of measurement should be objective. Obviously if one selects only the thinnest portion, or only the thickest portion of the basement membrane, one introduces a considerable error. I mention this because some investigators[9] measure only the thinnest portion of the basement membrane, and as we have recently documented,[10] this nonobjective procedure introduces a systematic error of approximately 30 to 40 percent. There is also an error in the objective random procedure of measuring all capillaries in that some capillaries will be obliquely sectioned. The resulting error, however, averages only a trivial 10 percent and for practical purposes can be ignored.

The results obtained by the QCBM method showed for the first time that persons with diabetes do in fact develop basement membrane thickening of their muscle capillaries—normal approximately 1,200 Angstrom units (Å), diabetic 2,400 Å.[7] This conclusion has subsequently been confirmed by everyone who has measured diabetic muscle capillaries.[11-15] The initial reports of Friederici and Schwartz[16] and Vracko,[17] indicating that there is no significant basement membrane thickening in diabetes, have both now been retracted.[13,18]

TABLE 1.—*Diagnostic Values for Muscle Capillary Basement Membranes*

←1,325 Å	1,600 Å→
Normal 96%	Normal 1%
Diabetic 1%	Diabetic 93%

TABLE 2.—*Prevalence of Muscle Capillary Basement Membrane Thickening in Adult Diabetes*

Author	*Year*	*Fixative*	*Number of Patients*	*Incidence Percent*
Siperstein ...	1968	Osmic	47/51	92
Vracko	1970	Osmic	9/9	100
Danowski-Fisher	1971	Osmic	9/9	100
Danowski-Fisher	1972	Osmic	6/6	100
Pardo	1972	Osmic	7/8	88
Siperstein ...	1973	Osmic	20/20	100
Williamson ..	1972	Glutaraldehyde	82/151	54
Yodaiken ...	1970	Glutaraldehyde	11/20	55
Siperstein ...	1973	Glutaraldehyde	9/20	45

Far more important from the standpoint of the clinician who wishes to use this method diagnostically, one must know the prevalence of this lesion in diabetic patients and how sensitive and accurate the procedure is (Table 1). The two critical figures in the QCBM technique are 1,325 and 1,600 Å (Table 1). Of normal subjects, 96 percent will fall below 1,325 Å, the false-negative error of the method is about 1 percent. By contrast, 93 percent of persons with diabetes have QCBM thickness greater than 1,600 Å and only 1 percent of normal biopsy specimens will yield false-positive results. The method then has proven to be extremely sensitive with an acceptable incidence of false-positive and negative values. All subsequent studies that have used this technique have confirmed these figures (Table 2). The two important points to emphasize in Table 2 are that these data are obtained in adults and second, that it is critical that the tissue be fixed in osmic acid.[10] As noted in Table 2, all investigators who fix their tissue in osmic acid find prevalence values for basement membrane thickening of from 88 to 100 percent. By contrast, if one fixes in glutaraldehyde, a very common and for most purposes an excellent electron microscopic fixative, one produces a relative

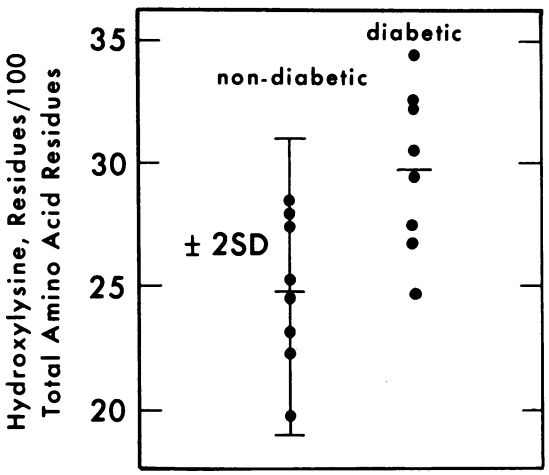

Chart 1.—Hydroxylysine in glomerular basement membrane (Beisswenger and Spiro, 1973[22]).

but variable swelling of the basement membranes and it becomes very difficult to measure. In part for this reason, the St. Louis group under Williamson finds only about half the prevalence of thickened basement membranes observed by our group. Yodaiken,[11] using glutaraldehyde fixation, also finds only a 55-percent prevalence of basement membrane hypertrophy, and in duplicate biopsy studies comparing both methods of fixation[10] we could confirm Williamson completely in that in glutaraldehyde-fixed tissues the sensitivity of the technique drops from the 92- to 100-percent prevalence observed in osmic acid fixation, to the point of detecting only roughly half of the persons with diabetes. So for this purpose it is critical, as everyone is finding, to fix tissues in osmic acid.

Biochemistry of Basement Membranes

The next question (which I wish to touch on only briefly, since we have so few answers in this field) is what is the underlying pathogenesis of basement membrane thickening and, hence, of diabetic microangiopathy? First, the thickening of the capillary basement membrane is clearly not accompanied by a thickening of the analogous structure that lines the muscle itself, in that the sarcolemma membrane lying only a few angstroms away from the capillary basement membrane escapes this lesion. One can frequently see collagenous fibers within the capillary basement membrane. Several biochemists, notably Lazarow,[19] Kefalides[20] and Spiro,[21] have analyzed basement membranes, and each has observed that basement membranes contain a high percentage of hydroxylysine and hydroxyproline. This structure, then, is made up of collagenous protein. One can in fact frequently see collagenous fibers within the capillary basement membrane. The major difference from structural collagen is that basement membranes contain a high fraction, approximately 10 percent, of carbohydrate. It had been hoped in our laboratory and by many other groups that some biochemical difference in amino acid structure between normal and diabetic basement membrane might be detected by suitable analysis. The only publication of such a finding is that of Beisswenger and Spiro,[22] who reported that diabetic basement membranes have a higher concentration of hydroxylysine than do normal basement membranes. As their data, shown in Chart 1, indicate, there is indeed a statistically significant difference in the mean hydroxylysine values of the eight diabetic and eight normal basement membranes. Unfortunately for the physiological implications of this observation, this difference depends entirely on the one high point in the diabetic group; moreover, only three of the eight diabetic subjects actually show significant differences in hydroxylysine. We have attempted to confirm this observation and have not succeeded;[23] moveover, three other groups have failed to find any difference in the amino acid composition of normal and diabetic basement membranes.[19,24,25] At this stage, therefore, we must conclude that there is simply no solid evidence to indicate a consistent biochemical change in the primary structure of the basement membrane of the diabetic kidney.

Limitations to the QCBM Method

From a theoretical standpoint it is also important to emphasize that basement membrane thickening in the patient with diabetes is not present at birth. As shown in Chart 2, recent studies in children have demonstrated that QCBM thickens with age in this younger group of diabetic patients,[26] less so in the age-matched control group, and then levels off in both groups at about age 20 (Chart 2). Below age 16 the prevalence of the lesion is not the 100 percent that one finds in adults. Depending on the age of the child, QCBM hypertrophy is seen in approximately 40 percent of young diabetic patients. It follows that a practical limitation of this technique is that in children a normal basement membrane width does

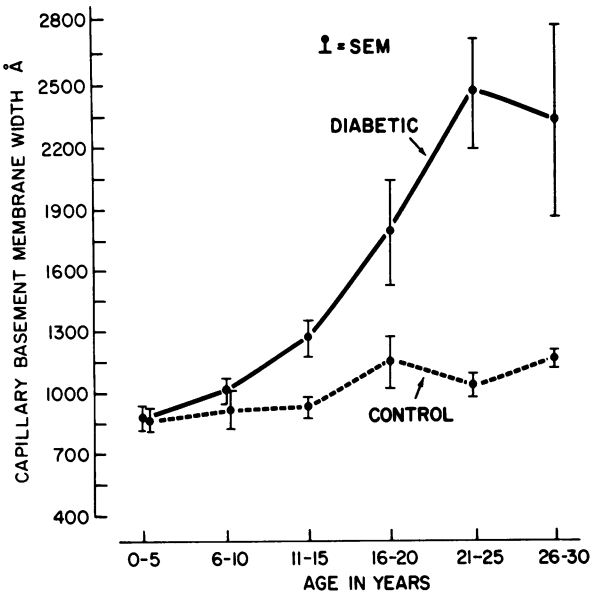

Chart 2.—QCBM width in diabetic and non-diabetic children.

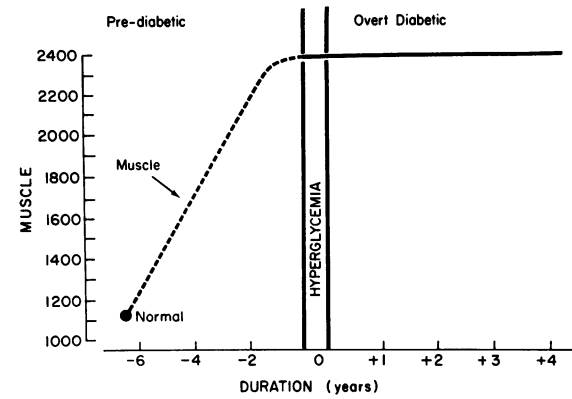

Chart 3.—Relation of muscle capillary basement membrane thickening to duration of diabetes.

not rule out the presence of diabetes mellitus, which for practical purposes such a finding would do in an adult.

There is a second interesting limitation of the QCBM method. That is, as indicated in Chart 3, there is no significant relationship between duration of diabetic hyperglycemia and QCBM width. This is of course a disadvantage of the technique, in that certainly in the kidney and probably, as indicated earlier, in the retina there is an effect of duration of hyperglycemia upon the vascular manifestations of diabetes. On the other hand, this finding does indicate that diabetic microangiopathy can be dissociated from the hyperglycemia of diabetes. Incidentally, were there a correlation between duration of hyperglycemia and basement membrane width, this relationship would in no way constitute evidence that hyperglycemia *causes* basement membrane thickening, as some investigators have suggested. Obviously, such concomitance would simply suggest that there is a relationship, which might indicate that basement membrane thickening causes hyperglycemia or that these two lesions of diabetes are progressing in response to some common biochemical defect, or that they might be independent.

The second point to be made from Chart 3 is that at the time of detection of diabetes mellitus, the width of the basement membrane is already maximal. Moreover, the 93 percent prevalence figure is observed at the time of onset of hyperglycemia, just as it is ten years later. In other

TABLE 3.—*Absence of Relationship of Duration of Hyperglycemia to Capillary Basement Membrane Width*

Duration in Years	*Investigator*	
	Siperstein A	*Williamson A ± SD*
0	2,497	1,268 ± 445
1-4	2,297	1,100 ± 220 NS
5-9	2,455	1,265 ± 432 NS
10-19	2,430	1,519 ± 628 NS
20+	2,706	1,802 ± 374 P<.01

words, there is no progression of the prevalence of QCBM thickness with duration of hyperglycemia. By contrast, Williamson's group[12] has suggested that there is a progression of basement membrane thickening with duration of hyperglycemia, a finding which, if valid, would of course significantly improve the value of this method. Williamson's data (Table 3), accepting the error caused by the measurement of only the minimal points of the basement membrane, actually show, as do ours, that there is no significant thickening of quadriceps capillary basement membrane for at least 20 years of hyperglycemia. After 20 years there may be some increase in quadriceps capillary basement membrane width, but at this late interval this finding is of little help in predicting basement membrane thickening in the kidney or in the retina.

Interestingly, Williamson's data also confirm our finding that the majority of persons with diabetes already have significant QCBM thickening at the time of onset of hyperglycemia. The QCBM method is therefore very sensitive because the basement membrane in the muscle is already maximally thickened at the time of onset of overt diabetes, but there is a disadvantage in that one cannot use this technique as a practical method of predicting what is going on in other tissues. Im-

plicit in this observation, as indicated by the dotted line in Chart 3, is the conclusion that muscle capillary basement membrane thickening actually occurs before the appearance of clinical hyperglycemia.

Data From Induced Hyperglycemia

The dissociation of the carbohydrate abnormalities of diabetes and diabetic microangiopathy can be studied in a number of ways. Perhaps the most common approach is to attempt to determine whether induced hyperglycemia in animals will produce basement membrane thickening. Actually the only published claim of quantitatively significant thickening of capillary basement membranes in response to induced hyperglycemia is that of Bloodworth.[27] These data show that there is in fact no significant thickening of renal basement membranes of dogs maintained hyperglycemic for up to four years ($3,111 \pm 413$ vs. $3,760 \pm 326$, $P > 0.1$). The same can be shown in the retina (Table 4). Bloodworth and Engerman's data[28] indicate that there is an insignificant difference in the retinal basement membrane width of dogs kept alloxan-hyperglycemic for many years. We have carried out similar experiments in monkeys that were kept hyperglycemic for 12 years by Dr. G. E. Gibbs, yet developed no basement membrane thickening.[29] In summary, there are probably no experiments indicating that hyperglycemia per se in animals will produce objective thickening of the capillary basement membranes.

The same experiment is performed rather regularly in man, in that man, too, frequently "pancreatectomizes" himself—with alcohol—and as a result produces secondary hyperglycemia. As Table 5 indicates, despite many years of such severe hyperglycemia only one of 18 subjects with pancreatogenous hyperglycemia has developed microangiopathy as detected by a thickening of the QCBM to a width greater than 1,600 Å. This result contrasts strikingly with the 93- to 100-percent prevalence of basement membrane thickening that one sees in genetic diabetes mellitus.

The observation that secondary hyperglycemia does not produce basement membrane thickening has now been confirmed in at least two other laboratories. Camerini-Davalos and Bloodworth[30] have also noted that basement membrane thickening does not develop in patients with Cushing's disease. Danowski and Fisher[15] have observed that many causes of secondary hyperglycemia, including muscular dystrophy and myotonia dystrophica, do not lead to basement membrane thickening. Danowski has termed such nondiabetic hyperglycemia "pseudodiabetes." I would prefer simply to drop the name diabetes and call such conditions nondiabetic or secondary hyperglycemia.

The finding that secondary hyperglycemia does not produce basement membrane thickening suggests a second very practical use of the QCBM technique. Dr. Richard Havel and I have collaborated on a study examining patients with lipodystrophic "diabetes"[7] and find that their basement membranes are normal. While hyperlipemia develops in diabetic patients, it is important clinically to recognize that hyperlipemia is an important cause of secondary hyperglycemia. We have recently[31]

TABLE 4.—*Retinal Capillary Basement Membrane Widths in Alloxan-Hyperglycemic Dogs*

(Age 6 years and over)
Bloodworth and Engerman, 1971

Hyperglycemia Å		*Control* Å	
3,000	3,150	3,400	3,250
1,875	2,200	3,000	1,900
2,300	2,900	2,800	2,700
2,475	3,400	2,750	2,500
5,100	3,500	2,300	1,800
2,450	4,100	2,195	
2,700	5,500		
Average 3,189 ± SE 286		2,600 ± SE 156	

"Diabetic" vs. Control = not significant

TABLE 5.—*Basement Membrane Width in Pancreatic "Diabetes"*

Age/Sex	*Diagnosis*	*FPS mg per 100 ml*	*Basement Membrane Width* Å
1. 24♂	Chronic Pancreatitis	531	1,219
2. 31♂	Chronic Pancreatitis	400	1,028
3. 41♂	Acute Pancreatitis	453	1,039
4. 45♂	Chronic Pancreatitis	200-300*	796
5. 45♂	Chronic Pancreatitis	298	2,344
6. 46♂	Chronic Pancreatitis	364	1,000
7. 49♂	Chronic Pancreatitis	320	1,428
8. 49♂	Chronic Pancreatitis	236/2 hr	1,167
9. 36♂	Chronic Pancreatitis	242	1,250
10. 50♂	Chronic Pancreatitis	236	1,066
11. 58♂	Chronic Pancreatitis	168	1,069
12. 38♂	Pancreatitis	250	865
13. 36♂	Acute and Chronic Pancreatitis	350	1,465
14. 46♂	Chronic Pancreatitis	490†	960
15. 48♂	Chronic Pancreatitis	290	951
16. 65♂	Chronic Pancreatitis	368	1,050
17. 30♂	Chronic Pancreatitis	340	1,040
18. 32♀	Chronic Pancreatitis	350	998
			Avg. 1,152

*Fasting hyperglycemia for 13 years.
†Fasting hyperglycemia for 6 years.

TABLE 6.—*Progression of Basement Membrane Thickening in a Prediabetic Patient*

Date	Glucose Tolerance F	1 hr	2 hr	Basement Membrane Width Å
1964	100	130	78	975 ± 102
1968	93	119	104	1,367 ± 88
1972	78	132	72	2,104 ± 222

shown that the QCBM method can be very useful in determining which patients do in fact have diabetes and which simply have hyperglycemia secondary to hyperlipemia.

What I have said up to this point is that neither in animals nor in man does hyperglycemia produce basement membrane thickening, a lesion which is for practical purposes a *sine qua non* of genetic diabetes mellitus. If, as we are implying, the carbohydrate abnormalities of diabetes really can be dissociated from the microangiopathy of diabetes, another way of looking at this relationship is to examine a group of genetically diabetic subjects in whom the carbohydrate abnormalities of diabetes have not yet developed. If diabetes is inherited as an autosomal recessive trait, it should ultimately develop in the offspring of two diabetic parents in all cases. If diabetes is inherited in a multifactorial manner, then according to Neel[32] approximately 75 percent of the offspring of two diabetic parents should ultimately become overtly diabetic. Whatever the mode of inheritance, the prevalence of diabetes in a group of offspring of two diabetic parents is high. We therefore selected some 30 prediabetic subjects, screened them carefully by repeated glucose tolerance tests and eliminated those who showed any abnormalities. Consequently, in these persons there are perfectly normal results from glucose tolerance tests, normal insulinogenic indices and normal growth hormone levels. But they did not have normal basement membranes.

Variance analysis is used in this study since the lesion does not start uniformly in every capillary nor uniformly around the circumference of each capillary; and variance analysis simply picks out such focal and segmental lesions. By this technique, 74 percent of the prediabetic subjects showed significant basement membrane thickening.[8] This finding led to the suggestion in 1968[7] that at least in adults the microangiopathy of diabetes may well precede the hyperglycemia of diabetes. A critical question that had to be asked is, "What happened to the 26 percent of prediabetic patients who did not have basement membrane thickening in the original study?" If followed over the years would microangiopathy also develop in these persons before the onset of carbohydrate abnormalities? We have then followed at least 21 of these patients over the past eight years. Data for one such patient are shown in Table 6.

Glucose tolerance measured in 1964 was perfectly normal and basement membrane width was also normal. By 1968 the basement membrane had begun to thicken despite the fact that the glucose tolerance remained normal. However, in 1972, the patient's basement membranes had thickened into the diabetic range (well above 1,600 Å). Results of a glucose tolerance test in 1972, if anything, were better than in 1964, but the basement membrane thickening was now unequivocal. A summary of the results in all such prediabetic patients indicates that both basement membrane width and prevalence of significant QCBM thickening increased over this eight year follow-up period; in fact, the prevalence of this lesion is now at 90 percent. We are therefore approaching in the prediabetic population the figure for QCBM hypertrophy that we see in the overtly diabetic patient. Incidentally, some five of these patients have now become diabetic as judged either by severe abnormalities in glucose tolerance or by development of overt diabetes mellitus.

This study then indicates that, first, if one does prospective studies on such prediabetic patients, basement membrane thickening does progress from that seen initially in prospective studies on such prediabetic patients and, second, ultimately some 90 percent of such prediabetic subjects will develop microangiopathy as detected by this technique. The question then arises as to whether microangiopathy is *clinically* detectable in prediabetic patients. We have recently screened all patients coming to a large ophthalmology clinic for any evidence of retinal microangiopathy.[33] Thirteen patients with such lesions but with normal glucose tolerance tests were examined by the quadriceps muscle capillary basement membrane method and eight were found to have significant basement membrane thickening. So by this independent measure we would suggest that clinically significant microangiopathy, too, may precede overt hyperglycemia in many more persons with diabetes than had previously been suspected. These patients will obviously have to be followed over the years to see whether in fact they develop overt diabetes mellitus, but this type

of data indicates that basement membrane thickening and microangiopathy of clinical significance may precede the hyperglycemia or detectable carbohydrate manifestations of diabetes mellitus.

Summary

The quantitative method of measurement of quadriceps capillary basement membrane width does provide a sensitive and reasonably specific means of objectifying diabetic microangiopathy, and gives one an independent marker for genetic diabetes mellitus. A second and important practical use of the technique is to differentiate secondary hyperglycemia from genetic diabetes mellitus. With the obvious genetic and pathologic differences in these two causes of hyperglycemia, this distinction becomes of increasing clinical significance.

Two limitations of the method must be emphasized. First, basement membrane thickening should not be used to diagnose prediabetes in individual patients. I think it is too early, despite the 90- or 74-percent figures, to use the technique in this way. Second, as we have repeatedly emphasized, the method does not predict the degree of microangiopathy in other tissues. I wish that Williamson's conclusion that the QCBM width is correlated with duration of hyperglycemia were correct, but I do not think it is. Third, one cannot use this procedure to rule out diabetes in young children. If the result is negative in a child, it does not mean, as it does in adults, that genetic diabetes mellitus is absent. If, on the other hand, the biopsy is positive, the lesion would have the same implications as it would in an adult.

From a theoretical standpoint, these observations strongly indicate that diabetic microangiopathy is independent of the carbohydrate abnormalities of diabetes mellitus. Whether basement membrane thickening may cause hyperglycemia is a far more complicated question. Obviously, if one implies that basement membrane thickening is truly primary, one must ask the question, "How can a thickening of the basement membrane cause hyperglycemia?" It is not surprising, as we have previously shown,[34] that capillaries supplying the islets of the pancreas also show this lesion. It is conceivable, therefore, that the microangiopathy that afflicts every other tissue of the body may by involving the islets of the pancreas influence the relationship of blood glucose to insulin secretion. The latter point is obviously still clearly speculative. At this time all that can be stated is that our data as well as those of Kilo and Williamson support the conclusion that hyperglycemia can be dissociated from, and so does not appear to be causally related to, the microangiopathy of diabetes.

The implications of these findings for the future I view rather optimistically. Clearly, if we know what causes basement membrane thickening we are going to be much closer to answering the question of what causes diabetic microangiopathy, be that microangiopathy independent of the carbohydrate abnormalities as I am suggesting, or even if caused by the carbohydrate abnormalities as is obviously still widely believed. But it is clear that only through an understanding of why basement membranes thicken in persons with diabetes will we one day be able to say what causes diabetic microangiopathy and, it is hoped, even what causes diabetes mellitus.

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American Medical Association to Sponsor 16th Conference on the Medical Aspects of Sports

THE 16TH CONFERENCE ON THE MEDICAL ASPECTS OF SPORTS, sponsored by the American Medical Association under the auspices of its Committee on the Medical Aspects of Sports, will be held in Portland, Oregon, at the Memorial Coliseum on Saturday, November 30, 1974. The Conference is held annually in conjunction with and on the first day of the Clinical Convention of the American Medical Association.

Major highlights of the 16th Conference will focus on: International sports medicine, Jesse Owens, and female athletics.

Additional topics to be discussed are: The effect of local steroid injections on tendon strength, hockey injuries, allied medical care, skiing safety progress, emergency first aid and comprehensive community programs.

The Conference is open to key athletic personnel, allied medical specialists, and interested physicians. For further information write:

THE COMMITTEE ON THE MEDICAL ASPECTS OF SPORTS
535 N. Dearborn St., Chicago, Illinois 60610